CURRENT THERAPEUTIC RESEARCH
VOLUME 67, NUMBER 3, MAY/JUNE 2006

Olprinone/Dopamine Combination for Improving Diaphragmatic Fatigue in Pentobarbital-Anesthetized Dogs

Yoshitaka Fujii, MD

Department of Anesthesiology, Institute of Clinical Medicine, University of Tsukuba, Tsukuba, Japan

ABSTRACT

Background: Diaphragmatic fatigue might contribute to the development of respiratory failure. In particular, the spontaneous, natural rate of phrenic nerve discharge occurs mainly in low-frequency ranges making low-frequency fatigue clinically important in both humans and animals. Olprinone, a phosphodiesterase 3 inhibitor, improves contractility in fatigued diaphragm, but is also associated with hypotension. Dopamine might be used concomitantly for treating related hypotension.

Objective: The purpose of the study was to assess the effect of olprinone plus dopamine on diaphragmatic fatigue in pentobarbital-anesthetized dogs.

Methods: This nonblinded study was conducted at the Department of Anesthesiology, Institute of Clinical Medicine, Tsukuba, Japan. Diaphragmatic fatigue (assessed by a decrease in diaphragmatic contractility) was induced by intermittent supramaximal bilateral electrophrenic stimulation at a frequency of 20 Hz applied for 30 minutes. Immediately after the fatigue-producing period, groups 2, 3, and 4 received an initial 10 μg/kg dose of olprinone. Group 2 then received maintenance olprinone of 0.3 μg/kg · min; group 3 received maintenance olprinone 0.3 μg/kg · min plus dopamine 2 μg/kg · min; and group 4 received maintenance olprinone 0.3 μg/kg · min plus dopamine 5 μg/kg · min. Group 1 received no study drug. Olprinone and dopamine were administered IV for 30 minutes. Diaphragmatic contractility was assessed by measuring the maximal transdiaphragmatic pressure (Pdi) generated by test stimuli after airway occlusion at functional residual capacity. Hypotension induced by the study drugs was defined as a >10 mm Hg decrease in mean arterial pressure (MAP), calculated by diastolic pressure plus 1/3 pulse pressure, from baseline.

Results: Twenty-eight mongrel dogs (18 males and 10 females, weighing 10–15 kg) were used in the study; 7 dogs were randomly assigned to each treatment group. When fatigue was established in each group, mean (SD) Pdi at low-frequency (20 Hz) stimulation decreased significantly from baseline in all groups (group 1: 15.6 [2.2] vs 11.7 [2.4] cm H_2O, $P = 0.008$; group 2: 15.4 [1.5] vs 11.6

Accepted for publication April 10, 2006.
doi:10.1016/j.curtheres.2006.06.003
0011-393X/06/$19.00

[1.3] cm H_2O, $P = 0.005$; group 3: 15.5 [2.0] vs 11.6 [1.8] cm H_2O, $P = 0.006$; group 4: 15.7 [1.4] vs 12.0 [1.4] cm H_2O, $P = 0.008$), while no significant change existed in Pdi at high-frequency (100 Hz) stimulation (P = NS). After study drug administration, Pdi in groups 2, 3, and 4 increased significantly from fatigued values at both 20 Hz stimulation (group 2: 11.6 [1.3] vs 21.8 [2.0] cm H_2O, $P = 0.001$; group 3: 11.6 [1.8] vs 22.2 [1.8] cm H_2O, $P = 0.001$; group 4: 12.0 [1.4] vs 25.9 [1.9] cm H_2O, $P = 0.001$) and 100 Hz stimulation (group 2: 22.0 [2.2] vs 29.0 [1.9] cm H_2O, $P = 0.002$; group 3: 22.1 [2.0] vs 29.3 [2.2] cm H_2O, $P = 0.002$; group 4: 21.8 [2.2] vs 31.7 [2.4] cm H_2O, $P = 0.001$). The increase in Pdi was significantly larger in group 4 compared with the other 3 groups (all, $P < 0.05$). Hypotension was not observed in group 4. MAP did not change significantly in group 1 or group 4 compared with baseline or fatigued MAP values (P = NS). Groups 2 and 3 had significant decreases in MAP with treatment compared with values in group 1 and with baseline and fatigued MAP values (all, $P < 0.05$). The MAP of group 4 was significantly greater than the MAP of groups 2 and 3 with treatment (both, $P < 0.05$).

Conclusions: Olprinone 0.3 μg/kg · min plus dopamine 5 μg/kg · min improved contractility in fatigued diaphragms and was not associated with hypotension in these pentobarbital-anesthetized dogs. Olprinone monotherapy and olprinone 0.3 μg/kg · min plus dopamine 2 μg/kg · min might improve contractility significantly. However, it was also associated with significant decreases in MAP. (*Curr Ther Res Clin Exp.* 2006;67:204–213) Copyright © 2006 Excerpta Medica, Inc.

Key words: muscle, diaphragm, contractility, fatigue, olprinone, dopamine, dogs, animal study.

INTRODUCTION

The diaphragm is the most important inspiratory muscle in the respiratory pumping system.[1,2] Fatigue of respiratory muscles, especially diaphragmatic fatigue, has been associated with respiratory failure in a variety of pulmonary diseases. Like methylxanthines, β_2-agonists, and digoxin,[3,4] phosphodiesterase 3 inhibitors (amrinone, milrinone, and olprinone) are effective in the treatment of diaphragmatic fatigue.[5–7] Among these phosphodiesterase 3 inhibitors, olprinone is the most efficacious,[5–7] but high-dose (>0.3 μg/kg · min) olprinone causes hypotension by its direct relaxing effect on the vascular smooth muscle.[8] This hypotension might increase the risk of organ dysfunction, including brain ischemia, myocardial ischemia, and decreased renal blood flow, especially in elderly or ill patients.[9] Dopamine directly stimulates α- and β-adrenergic receptors; it is most often used in clinical situations characterized by decreased systemic blood pressure.[10] Therefore, dopamine might prevent hypotension induced by olprinone. Also, dopamine has been associated with an increase in diaphragmatic strength in patients with chronic obstructive pulmonary disease during treatment for acute respiratory failure.[11] However, based on a MEDLINE search (key words: *olprinone*, *dopamine*, *muscle*, *diaphragm*, *contractility*, and *fatigue*; years: January 1990–February 2006), published

data regarding the possible effects of the combination of olprinone and dopamine on diaphragmatic fatigue in animals or humans was not found.

This study was undertaken to assess the efficacy of olprinone plus dopamine in treating diaphragmatic fatigue in pentobarbital-anesthetized dogs.

MATERIALS AND METHODS

This study was conducted at the Department of Anesthesiology, Institute of Clinical Medicine, University of Tsukuba, Tsukuba, Japan. The protocol was approved by our animal research committee, and the care of animals was conducted in agreement with guidelines for ethical animal research.[6,7] The author, who was not blinded to treatment group, performed all measurements and analyses in the study.

Adult (>5 years) mongrel dogs (provided by Animal Guidance Center, Mashiko, Japan) were randomly assigned to 1 of 4 study groups using a computer-generated (StatView, SAS Institute Inc., Tokyo, Japan) list of random numbers: group 1, no study drug; group 2, olprinone 0.3 μg/kg · min; group 3, olprinone plus dopamine 2 μg/kg · min; and group 4, olprinone plus dopamine 5 μg/kg · min.

Animal preparation was similar to that described previously.[5–7] Briefly, anesthesia was maintained with IV pentobarbital 2 mg/kg · h. No muscle relaxant was used. Each dog's trachea was intubated, and ventilation was mechanically controlled with a mixture of oxygen and air (40% inspired oxygen) to maintain arterial partial pressure of oxygen >100 mm Hg, arterial partial pressure of carbon dioxide 35 to 40 mm Hg, and arterial pH 7.35 to 7.45. The right femoral artery was cannulated to monitor arterial blood pressure and the right femoral vein was cannulated to administer maintenance fluid. The left femoral vein was cannulated to administer the study drugs (olprinone, dopamine). A flow-directed pulmonary artery catheter was advanced via the right external jugular vein into the pulmonary artery to measure cardiac output (CO) using the thermodilution technique.[12] Transdiaphragmatic pressure (Pdi) was measured using 2 thin-walled latex balloons: 1 was positioned in the stomach and the other in the middle third of the esophagus. The balloons were connected to a differential pressure transducer (TP 604T, Nihon Koden, Tokyo, Japan) and an amplifier (model 1257, Nihondenki San-ei, Tokyo, Japan). Phrenic nerves were exposed bilaterally at the neck, and stimulating electrodes were placed around them. Supramaximal electrical stimuli (10–15 V) of 0.1 ms duration were applied for 2 seconds at low frequency (20 Hz) and high frequency (100 Hz) with an electrical stimulator (SEN-3301, Nihon Koden). Diaphragmatic contractility was then assessed by measuring the maximal Pdi generated by the test stimuli after airway occlusion at functional residual capacity. Electrical activity of the diaphragm was recorded using 2 pairs of fishhook electrodes. Activity signals from the diaphragm were rectified and integrated with an integrator (type 1322, Nohondenki San-ei) with a time constant of 0.1 second. This was regarded as the integrated activity of the crural (Edi-cru) and costal (Edi-cost) parts of the diaphragm.

The dogs were allowed to stabilize for at least 30 minutes before study initiation following animal preparation. Baseline measurements of Pdi, Edi-cru, Edi-cost, and hemodynamic variables (heart rate [HR], mean arterial pressure [MAP], right atrial pressure [RAP], mean pulmonary arterial pressure [MPAP], pulmonary artery occlusion pressure [PAOP], and CO) were recorded in each group. RAP, MPAP, and PAOP were measured by using a pulmonary artery catheter. Diaphragmatic fatigue was induced by intermittent supramaximal bilateral electrophrenic stimulation applied for 30 minutes at a frequency of 20 Hz (entire cycle lasting for 4 seconds with a duty cycle of 0.5 second [ie, low-frequency fatigue]).[13] When fatigue was established (assessed by a decrease in diaphragmatic contractility), groups 2, 3, and 4 received continuous IV olprinone (10 μg/kg initial dose plus 0.3 μg/kg · min maintenance dose) with an electrical infusion pump for 30 minutes. During olprinone administration, group 3 received dopamine 2 μg/kg · min and group 4 received dopamine 5 μg/kg · min, both by IV infusion.

Immediately after the cessation of study drug administration, Pdi, Edi-cru, Edi-cost, HR, MAP, RAP, MPAP, PAOP, and CO were measured. Though no study drug was administered to group 1, the same measurements were performed as in the other groups. Hypotension was defined as a >10 mm Hg decrease in MAP from baseline. The changes in Edi-cru (%Edi-cru) and Edi-cost (%Edi-cost) from baseline were also determined.

Statistical Analysis

Values are given as mean (SD). Statistical analyses were performed using analysis of variance for repeated measurements followed by the Bonferroni adjustment and Dunn test for multiple comparisons and the Student *t* test, as appropriate. $P < 0.05$ was considered significant. A power analysis was performed to determine the number of animals needed in this experiment, based on the following: (1) improvement in contractility of fatigued diaphragm during study drug administration (primary end point); (2) occurrence of hypotension induced by study drug (secondary end point); and (3) $\alpha = 0.05$ with a power $(1 - \beta) = 0.8$. Based on these requirements, a total of 7 dogs per group was determined to be sufficient. Analyses were performed using SPSS version 8.0 (SPSS Inc., Chicago, Illinois).

RESULTS

Twenty-eight adult mongrel dogs (18 males and 10 females, weighing 10–15 kg) were included in the study; 7 dogs were assigned to each treatment group. No significant differences in baseline hemodynamic variables were observed among the groups. With an infusion of olprinone alone (group 2) or in combination with dopamine 2 μg/kg · min (group 3), HR and CO levels increased significantly (all, $P < 0.05$) while MAP, MPAP, and PAOP decreased significantly (all, $P < 0.05$) from baseline. After administering olprinone plus

dopamine 5 μg/kg · min (group 4), HR and CO increased significantly (HR: 142 [11] vs 160 [11] bpm, $P = 0.007$; CO: 1.9 [0.2] vs 3.5 [0.2] L/min, $P = 0.001$), while there was no significant difference from baseline in MAP, MPAP, and PAOP (all, P = NS). Hypotension was not observed in group 4. No hemodynamic changes were observed in group 1. After treatment, groups 2 and 3 had significant decreases in MAP compared with fatigued values (121 [10] vs 107 [10] mm Hg, $P = 0.022$ and 122 [9] vs 109 [11] mm Hg, $P = 0.023$, respectively) and group 1 MAP values (123 [9] vs 107 [10] and 123 [9] vs 109 [11] mm Hg; both, $P = 0.019$). The posttreatment MAP of group 4 (124 [10] mm Hg) was significantly greater than that of group 2 (107 [10] mm Hg) and group 3 (109 [11] mm Hg; both, $P < 0.05$) (**Table I**).

The Pdi, %Edi-cru, and %Edi-cost values obtained for all 4 groups at low- and high-frequency stimulation are shown in **Table II**. When fatigue was established in each group, Pdi at low-frequency (20 Hz) stimulation decreased significantly from baseline in all groups ($P < 0.05$), while Pdi at high-frequency (100 Hz) stimulation did not change significantly (P = NS). After treatment, Pdi at both stimuli levels increased significantly from fatigued values in groups 2, 3, and 4 ($P < 0.05$). The increase in Pdi at both stimuli levels was significantly greater in group 4 than in the other 3 groups (all, $P < 0.05$). In group 1, which received no study drugs, Pdi at 20 Hz stimulation did not increase from fatigued values (P = NS). No changes in %Edi-cru and %Edi-cost at either stimulation level were observed in any group throughout the experiment.

DISCUSSION

The spontaneous, natural rate of phrenic nerve discharge occurs mainly in the low-frequency ranges (ie, 5–30 Hz), making low-frequency fatigue of particular clinical importance.[14] In this study, therefore, the effects of olprinone monotherapy, or olprinone in combination with dopamine, on contractility during diaphragmatic fatigue induced by 20 Hz stimulation (ie, low-frequency fatigue) were studied. In group 1, which received no study drugs, diaphragmatic contractility (assessed by Pdi) at 20 Hz stimulation did not increase from fatigued values. These results were in agreement with previous studies we have conducted.[5–7] Because the dogs were anesthetized with pentobarbital, the combined effects of pentobarbital and the study drugs on diaphragmatic contractility were also examined. However, it has been reported that pentobarbital, in the dose used in this experiment (2 mg/kg · h), does not affect contractility of the diaphragm.[15] This was in accordance with our findings that pentobarbital-anesthetized dogs that did not receive a study drug were associated with no significant change in Pdi after fatigue was established.

Olprinone increases cardiac muscle contractility by selectively inhibiting phosphodiesterase 3 and accumulating cyclic adenosine monophosphate intracellularly, which induces the activation of the calcium ion (Ca^{2+}) transport from the sarcoplasmic reticulum.[16,17] In addition to these pharmacologic properties,

Table I. Mean (SD) hemodynamic data at baseline, in fatigued diaphragm, and after treatment in pentobarbital-anesthetized dogs in group 1 (no study drug), group 2 (olprinone 0.3 μg/kg · min), group 3 (olprinone plus dopamine 2 μg/kg · min), and group 4 (olprinone plus dopamine 5 μg/kg · min) (N = 28). Groups 2, 3, and 4 received an inital 10 μg/kg dose of olprinone.

Variable	Group	Baseline	Fatigued Diaphragm	After Treatment
HR, bpm	1	142 (10)	140 (12)	140 (10)
	2	140 (10)	140 (8)	152 (6)*†‡
	3	140 (11)	139 (10)	153 (10)*†‡
	4	142 (11)	141 (11)	160 (11)*†‡
MAP, mm Hg	1	123 (8)	123 (8)	123 (9)
	2	122 (8)	121 (10)	107 (10)*†‡
	3	121 (10)	122 (9)	109 (11)*†‡
	4	123 (7)	123 (9)	124 (10)§‖
RAP, mm Hg	1	5 (2)	5 (2)	5 (2)
	2	5 (1)	5 (2)	5 (2)
	3	5 (1)	5 (1)	5 (1)
	4	5 (2)	5 (2)	5 (2)
MPAP, mm Hg	1	12 (2)	12 (1)	12 (2)
	2	12 (1)	12 (2)	10 (1)*†‡
	3	12 (1)	12 (2)	10 (1)*†‡
	4	12 (1)	12 (2)	12 (1)§‖
PAOP, mm Hg	1	8 (2)	8 (2)	8 (2)
	2	8 (2)	8 (1)	6 (1)*†‡
	3	8 (2)	8 (1)	6 (1)*†‡
	4	8 (2)	8 (1)	8 (2)§‖
CO, L/min	1	2.0 (0.2)	2.0 (0.3)	2.0 (0.3)
	2	2.1 (0.4)	2.1 (0.4)	3.0 (0.4)*†‡
	3	2.0 (0.3)	2.1 (0.3)	3.1 (0.3)*†‡
	4	1.9 (0.2)	2.0 (0.2)	3.5 (0.2)*†‡§‖

HR = heart rate; MAP = mean arterial pressure; RAP = right atrial pressure; MPAP = mean pulmonary arterial pressure; PAOP = pulmonary artery occlusion pressure; CO = cardiac output.
*$P < 0.05$ versus baseline.
†$P < 0.05$ versus fatigued diaphragm.
‡$P < 0.05$ versus group 1.
§$P < 0.05$ versus group 2.
‖$P < 0.05$ versus group 3.

Table II. Mean (SD) changes in transdiaphragmatic pressure (Pdi), electrical activity of the crural part of the diaphragm (%Edi-cru), and electrical activity of the costal part of the diaphragm (%Edi-cost) at baseline, in fatigued diaphragm, and after treatment in group 1 (no study drug), group 2 (olprinone 0.3 µg/kg · min), group 3 (olprinone plus dopamine 2 µg/kg · min), and group 4 (olprinone plus dopamine 5 µg/kg · min) (N = 28). Groups 2, 3, and 4 received an intial 10 µg/kg dose of olprinone.

Variable	Group	Baseline	Fatigued Diaphragm	After Treatment
Pdi, cm H_2O				
20 Hz stimulation	1	15.6 (2.2)	11.7 (2.4)*	11.9 (2.5)*
	2	15.4 (1.5)	11.6 (1.3)*	21.8 (2.0)*†‡
	3	15.5 (2.0)	11.6 (1.8)*	22.2 (1.8)*†‡
	4	15.7 (1.4)	12.0 (1.4)*	25.9 (1.9)*†‡§‖
100 Hz stimulation	1	22.1 (2.4)	21.9 (2.3)	22.0 (2.1)
	2	22.1 (2.0)	22.0 (2.2)	29.0 (1.9)*†‡
	3	22.2 (1.9)	22.1 (2.0)	29.3 (2.2)*†‡
	4	22.0 (2.2)	21.8 (2.2)	31.7 (2.4)*†‡§‖
%Edi-cru				
20 Hz stimulation	1	100 (0.0)	99.1 (6.1)	99.1 (6.1)
	2	100 (0.0)	99.1 (6.1)	100.2 (5.2)
	3	100 (0.0)	97.9 (3.9)	101.4 (3.8)
	4	100 (0.0)	98.9 (3.0)	100.2 (5.2)
100 Hz stimulation	1	100 (0.0)	99.6 (2.1)	99.6 (2.1)
	2	100 (0.0)	98.9 (2.0)	99.4 (2.5)
	3	100 (0.0)	99.4 (2.5)	99.4 (2.5)
	4	100 (0.0)	99.8 (2.0)	99.8 (2.0)
%Edi-cost				
20 Hz stimulation	1	100 (0.0)	98.9 (3.0)	98.9 (3.0)
	2	100 (0.0)	99.1 (6.1)	99.1 (6.1)
	3	100 (0.0)	98.6 (3.9)	99.1 (6.1)
	4	100 (0.0)	99.1 (3.0)	100.2 (5.2)
100 Hz stimulation	1	100 (0.0)	99.8 (2.0)	99.8 (2.0)
	2	100 (0.0)	98.9 (2.0)	99.6 (2.1)
	3	100 (0.0)	99.4 (2.5)	99.4 (2.5)
	4	100 (0.0)	99.8 (2.0)	99.8 (2.0)

*$P < 0.05$ versus baseline.
†$P < 0.05$ versus fatigued diaphragm.
‡$P < 0.05$ versus group 1.
§$P < 0.05$ versus group 2.
‖$P < 0.05$ versus group 3.

olprinone might be useful for improving contractility in a fatigued diaphragm.[7] In the present study, we showed that Pdi at 20 Hz and 100 Hz stimulation increased significantly from fatigued values (both, $P < 0.05$) with an infusion of olprinone (group 2). In preliminary studies we performed,[7,18] to clarify the mechanism responsible for the efficacy of olprinone in augmenting contractility of fatigued diaphragm, the combination of olprinone and nicardipine, a calcium channel blocker that inhibits Ca^{2+} influx into the diaphragm muscle, was administered. We found that the enhanced diaphragmatic contractility with olprinone was abolished with an infusion of nicardipine, suggesting that olprinone increases contractility in a fatigued diaphragm by influencing Ca^{2+} transport across the cell membrane.

It is known that olprinone produces positive inotropic and vasodilating effects,[16,17] thereby inducing severe hypotension during high-dose (>0.3 μg/kg · min) olprinone administration.[8] To avoid hypotension, dopamine was added to olprinone in the present study. In group 3 (olprinone 0.3 μg/kg · min plus dopamine 2 μg/kg · min), MAP decreased significantly from baseline ($P < 0.05$) and Pdi at 20 Hz and 100 Hz stimulation increased significantly from fatigued values (both, $P < 0.05$). In group 4 (olprinone 0.3 μg/kg · min plus dopamine 5 μg/kg · min), MAP did not decrease from baseline and Pdi at both stimuli increased significantly from fatigued values (both, $P < 0.05$). Therefore, in this study, the addition of dopamine 5 μg/kg · min was associated with the prevention of hypotension caused by olprinone therapy.

We also found that Pdi at 20 Hz and 100 Hz stimulation increased significantly from fatigued values with an infusion of olprinone alone and combined with dopamine and that the increases in Pdi were largest when the study drugs were combined. These findings suggest that dopamine added to olprinone increases the contractility of fatigued diaphragm in a dose-dependent manner. The precise mechanism underlying these findings is unknown. Diaphragmatic contractility depends on the energy supplied to the diaphragm, which is related to the blood supply to the diaphragm. CO is one of the major factors for determining blood flow to the diaphragm.[19] Diaphragmatic fatigue occurs when more energy is used by the muscles than is supplied by the blood.[17] Therefore, the increase in CO we observed in groups 2, 3, and 4 might have led to an increase in blood flow to the diaphragm, which might have then increased the contractility of fatigued diaphragm by increasing oxygen delivery to the diaphragm.

Our findings on improving diaphragmatic fatigue by administering olprinone monotherapy and in combination with dopamine must be considered within the context of the study limitations. Diaphragmatic fatigue occurs in a number of clinical conditions in which the work of breathing is increased, such as airway obstruction, asthma, or chronic obstructive pulmonary disease.[1,2] In this study, diaphragmatic fatigue was induced by intermittent supramaximal bilateral electrophrenic stimulation at a frequency of 20 Hz,[11] which differs from the fatigue produced by certain pathological conditions.[1,2] The experimental fatigue of the diaphragm was not associated with an increased load of the air-

way. We have already assessed the effect of olprinone on diaphragm muscle function during fatigue induced by 20 Hz stimulation.[7] Also, blood flow to the diaphragm, which can affect diaphragmatic contractility, was not measured in the present study. However, Aubier et al[11] found that dopamine 10 μg/kg · min increased both diaphragmatic blood flow (assessed by timed volume collections of the inferior phrenic venous effluent) and diaphragmatic contractility (assessed by Pdi). Another limitation of the study was our small sample size. However, when power analysis was performed, a total of 7 dogs in each group was found to be sufficient to detect a significant difference with α of 0.05 and 80% power of the study. Lastly, the study was not blinded. Further studies should consider these limitations.

CONCLUSIONS

Olprinone treatment administered concomitantly with dopamine 5 μg/kg · min improved contractility in fatigued diaphragms and was not associated with hypotension in pentobarbital-anesthetized dogs. In this study, olprinone monotherapy or olprinone 0.3 μg/kg · min plus dopamine 2 μg/kg · min improved contractility significantly. It was also associated with significant decreases in MAP.

REFERENCES

1. Macklem PT, Roussos CS. Respiratory muscle fatigue: A cause of respiratory failure? *Clin Sci Mol Med.* 1977;53:419–422.
2. Cohen CA, Zagelbaum G, Gross D, et al. Clinical manifestations of inspiratory muscle fatigue. *Am J Med.* 1982;73:308–316.
3. Howell S, Roussos C. Isoproterenol and aminophylline improve contractility of fatigued canine diaphragm. *Am Rev Respir Dis.* 1984;129:118–124.
4. Aubier M, Viires N, Murciano D, et al. Effects of digoxin on diaphragmatic strength generation. *J Appl Physiol.* 1986;61:1767–1774.
5. Fujii Y, Toyooka H, Amaha K. Amrinone improves contractility of fatigued diaphragm in dogs. *Can J Anaesth.* 1995;42:80–86.
6. Fujii Y, Takahashi S, Toyooka H. The effects of milrinone and its mechanism in the fatigued diaphragm in dogs. *Anesth Analg.* 1998;87:1077–1082.
7. Fujii Y, Takahashi S, Toyooka H. The effect of olprinone compared with milrinone on diaphragmatic muscle function in dogs. *Anesth Analg.* 1999;89:781–785.
8. Kimata S, Hirosawa K, Kasanuki H, et al. Clinical effects of olprinone on acute heart failure: Optimal dose-finding study [in Japanese]. *Jpn J Clin Exp Med.* 1992;69:3984–3996.
9. Arai T. Effects of olprinone hydrochloride after coronary artery bypass grafting [in Japanese]. *Masui.* 2004;53:122–130.
10. Hoffman BB, Lefkowitz RJ. Catecholamines, sympathomimetric drugs, and adrenergic receptor antagonist. In: Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, eds. *Goodman & Gilman's the Pharmacological Basis of Therapeutics.* 9th ed. New York, NY: McGraw-Hill; 1996:199–248.
11. Aubier M, Murciano D, Menu Y, et al. Dopamine effects on diaphragmatic strength during acute respiratory failure in chronic obstructive pulmonary disease. *Ann Intern Med.* 1989;110:17–23.

12. Vender JS, Gilbert HC. Monitoring the anesthetized patient. In: Barash PG, Cullen BF, Stoelting RK, eds. *Clinical Anesthesia.* 3rd ed. Philadelphia, Pa: Lippincott-Raven; 1996:621–641.
13. Aubier M, Farkas G, De Troyer A, et al. Detection of diaphragmatic fatigue in man by phrenic stimulation. *J Appl Physiol.* 1981;50:538–544.
14. Roussos C, Macklem PT. The respiratory muscles. *N Engl J Med.* 1982;307:786–797.
15. Ide T, Kochi T, Isono S, Mizuguchi T. Effect of sevoflurane on diaphragmatic contractility in dogs. *Anesth Analg.* 1992;74:739–746.
16. Ogawa T, Ohhara H, Tsunoda H, et al. Cardiovascular effects of the new cardiotonic agent 1,2-dihydro-6-methyl-2-oxo-5-(imidazo[1,2-a]pyridin-6-yl)-3-pyridine carbonitrile hydrochloride monohydrate. 1st communication: Studies on isolated guinea pig cardiac muscles. *Arzneimittelforschung.* 1989;39:33–37.
17. Ohhara H, Ogawa T, Takeda M, et al. Cardiovascular effects of the new cardiotonic agent 1,2-dihydro-6-methyl-2-oxo-5-(imidazo[1,2-a]pyridin-6-yl)-3-pyridine carbonitrile hydrochloride monohydrate. 2nd Communication: Studies in dogs. *Arzneimittelforschung.* 1989;39:38–45.
18. Fujii Y, Toyooka H, Amaha K. Nicardipine enhances diaphragmatic fatigue. *Can J Anaesth.* 1994;41:435–439.
19. Robertson CH Jr, Foster GH, Johnson RL Jr. The relationship of respiratory failure to the oxygen consumption of, lactate production by, and distribution of blood flow among respiratory muscles during increasing inspiratory resistance. *J Clin Invest.* 1977;59:31–42.

Address correspondence to: Yoshitaka Fujii, MD, First Department of Anesthesiology, Toho University School of Medicine, 6-11-1, Ohmori-Nishi, Ohta-ku, Tokyo 143-8541, Japan. E-mail: yfujii@med.toho-u.ac.jp